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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * * *

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=>
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L1      STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS
L1                STR
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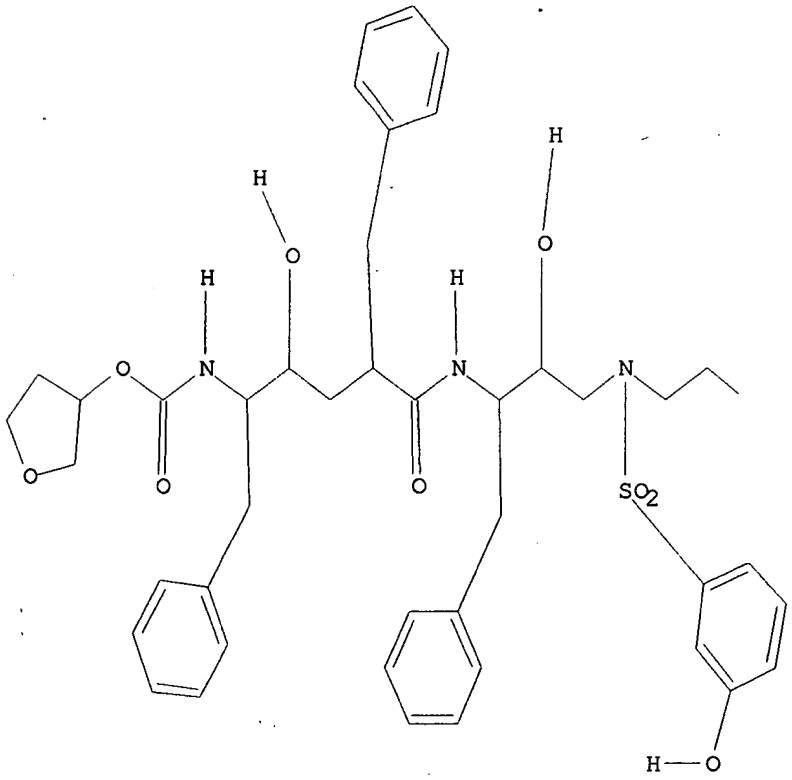


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Structure attributes must be viewed using STN Express query preparation.


=> s l1 full

L3             0 SEA SSS FUL L1

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L4      STRUCTURE UPLOADED

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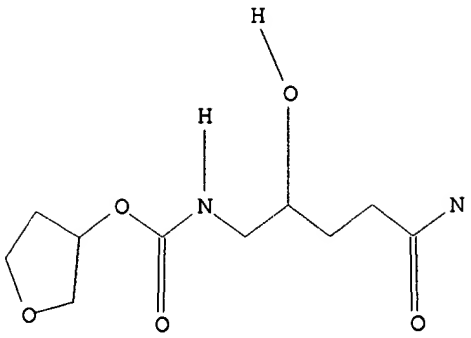
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l4 full

L6 66 SEA SSS FUL L4

=> file ca

=> s l6

L7 13 L6

=> s l7 and hiv

32440 HIV
L8 12 L7 AND HIV

=> d ibib abs fhitstr hitrn 1-12

L8 ANSWER 1 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 131:223019 CA
TITLE: GA strategy for variable selection in QSAR studies. Enhancement of comparative molecular binding energy analysis by GA-based PLS method
AUTHOR(S): Hasegawa, Kiyoshi; Kimura, Toshiro; Funatsu, Kimito
CORPORATE SOURCE: Tokyo Research Laboratories, Kowa Co. Ltd., Higashimurayama, 189, Japan
SOURCE: Quant. Struct.-Act. Relat. (1999), 18(3), 262-272
CODEN: QSARDI; ISSN: 0931-8771
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A study was performed to examine whether genetic algorithm-based partial least squares (GAPLS) developed for variable selection can enhance prediction and interpretation of the comparative mol. binding energy (COMBINE) model. Structure-activity data of inhibitors of **HIV**-1 protease were used as a test example. By applying GAPLS to this data set,

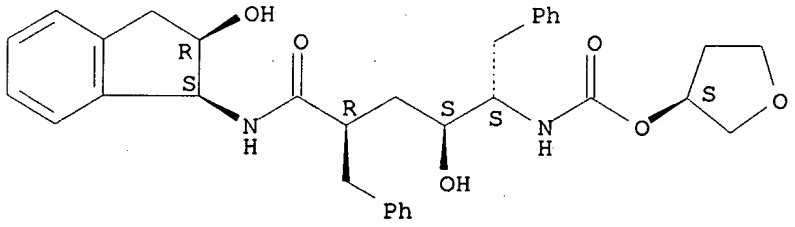
several improved PLS models with a high cross-validated r2 value and low no. of variables were obtained. To select a best model from them, external validation was performed for each model. The finally selected model was further examd. by comparing with the 3D structure of **HIV** -1 protease in computer graphics and its agreement was confirmed.

IT **145631-03-4**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibitory activity on **HIV**-1 protease by genetic algorithm-based partial least squares method)

RN 145631-03-4 CA

CN Carbamic acid, [(1S,2S,4R)-5-[[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, (3S)-tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145631-03-4**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibitory activity on **HIV**-1 protease by genetic algorithm-based partial least squares method)

REFERENCE COUNT: 27
REFERENCE(S): CA
(1) Baroni, M; Quant Struct Act Relat 1993, V12, P9 CA
(2) Clark, M; Quant Struct Act Relat 1993, V12, P137 CA
(3) Cramer, R; J Amer Chem Soc 1988, V110, P5959 CA
(5) Fujita, T; Quant Struct-Act Relat 1997, V16, P107 CA
(6) Geladi, P; Anal Chim Acta 1986, V185, P1 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 129:239460 CA
TITLE: Simulation of alternative binding modes in a structure-based QSAR study of **HIV**-1 protease inhibitors
AUTHOR(S): Pastor, Manuel; Perez, Carlos; Gago, Federico
CORPORATE SOURCE: Department of Pharmacology, University of Alcala, Alcala de Henares, E-28871, Spain
SOURCE: J. Mol. Graphics Modell. (1998), Volume Date 1997, 15(6), 364-371
CODEN: JMGMFI; ISSN: 1093-3263
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have used a published set of inhibitors of **HIV**-1 protease to build a COMBINE-type structure-based QSAR model with good predictive

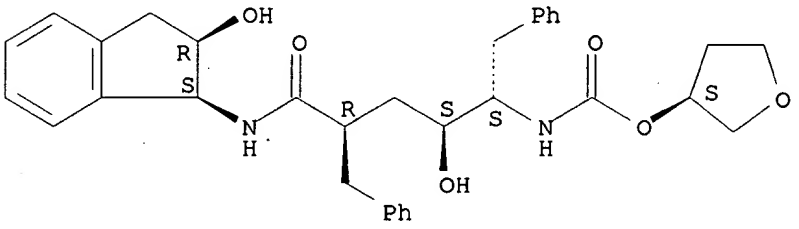
ability (r2 = 0.90, q2 = 0.69).2. Since the compds. in the training series exhibit most of their structural variability on one-half of the pseudosym. binding cavity and only one binding orientation was explored for each mol., the model describes mainly the effect of the structural changes on interactions involving only one-half of the binding cavity (pockets S1' and 2'). Thus, the model cannot be expected to give accurate predictions for new compds. exhibiting structural variation in both halves. The model does in fact show a tendency to underpredict slightly the biol. activity of the mols. in the external test set. In an attempt to improve the quality of the model, both possible orientations of the ligands are now considered so that structural variation takes place in all binding pockets. One possibility would have been to build an addnl. set of complexes with the inhibitors docked in a reversed orientation. The alternative we have explored, however, consists of manipulating the data matrix describing the interaction energies so that each row is duplicated and the order of the variables in the duplicated rows is swapped between subunits. This simple approach has produced a new model that is similar in quality to the original model (r2 = 0.89, q2 = 0.64) but lacks the tendency to underpredict the activity of the compds. in the external set. Moreover, since equiv. residues are assigned equiv. wts., the model is insensitive to ligand orientation and is easier to interpret.

IT **145631-03-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(simulation of alternative binding modes in a structure-based QSAR study of **HIV**-1 protease inhibitors)

RN 145631-03-4 CA

CN Carbamic acid, [(1S,2S,4R)-5-[[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, (3S)-tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145631-03-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(simulation of alternative binding modes in a structure-based QSAR study of **HIV**-1 protease inhibitors)

L8 ANSWER 3 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 128:212673 CA
TITLE: Comparative Binding Energy Analysis of **HIV**-1 Protease Inhibitors: Incorporation of Solvent Effects and Validation as a Powerful Tool in Receptor-Based Drug Design
AUTHOR(S): Perez, Carlos; Pastor, Manuel; Ortiz, Angel R.; Gago, Federico

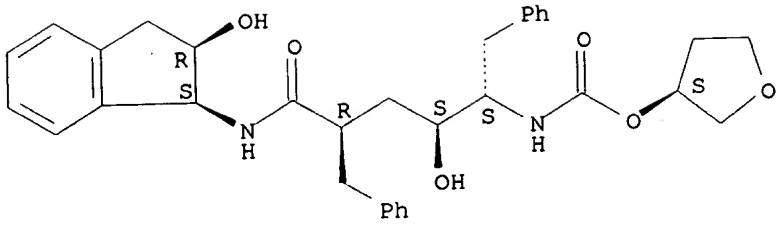
CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Alcala, E-28871, Spain
SOURCE: J. Med. Chem. (1998), 41(6), 836-852
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A comparative binding energy (COMBINE) anal. was performed on a training set of 33 **HIV**-1 protease inhibitors, and the resulting regression models were validated using an addnl. external set of 16 inhibitors. This data set was originally reported by Holloway et al. (1995), who showed the usefulness of mol. mechanics interaction energies for predicting the activity of novel **HIV**-1 protease inhibitors within the framework of the MM2X force field and linear regression techniques. The authors first used the AMBER force field on the same set of 3-dimensional structures to check up on any possible force-field dependencies. In agreement with the previous findings, the calcd. raw ligand-receptor interaction energies were highly correlated with the inhibitory activities (r2 = 0.81), and the linear regression model relating both magnitudes had an acceptable predictive ability both in internal validation tests (q2 = 0.79, SDEPcv = 0.61) and when applied to the external set of 16 different inhibitors (SDEPex = 1.08). When the interaction energies were further analyzed using the COMBINE formalism, the resulting PLS model showed improved fitting properties (r2 = 0.89) and provided better estns. for the activity of the compds. in the external data set (SDEPex = 0.83). Computation of the electrostatic part of the ligand-receptor interactions by numerically solving the Poisson-Boltzmann equation did not improve the quality of the linear regression model. On the contrary, incorporation of the solvent-screened residue-based electrostatic interactions and 2 addnl. descriptors representing the electrostatic energy contributions to the partial desolvation of both the ligands and the receptor resulted in a COMBINE model that achieved a remarkable predictive ability, as assessed by both internal (q2 = 0.73, SDEPcv = 0.69) and external validation tests (SDEPex = 0.59). Finally, when all the inhibitors studied were merged into a single expanded set, a new model was obtained that explained 91% of the variance in biol. activity (r2 = 0.91), with very high predictive ability (q2 = 0.81, SDEPcv = 0.66). In addn., the COMBINE anal. provided valuable information about the relative importance of the contributions to the activity of individual residues that can be fruitfully used to design better inhibitors. All in all, COMBINE anal. is validated as a powerful methodol. for predicting binding affinities and pharmacol. activities of congeneric ligands that bind to a common receptor.

IT **145631-03-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(solvent effects on comparative binding energy anal. of **HIV** protease inhibitors in receptor-based drug design)

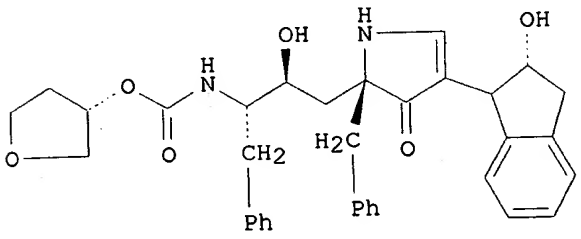
RN 145631-03-4 CA
CN Carbamic acid, [(1S,2S,4R)-5-[[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, (3S)-tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145631-03-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(solvent effects on comparative binding energy anal. of **HIV** protease inhibitors in receptor-based drug design)

L8 ANSWER 4 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 127:130483 CA
TITLE: An Orally Bioavailable Pyrrolinone Inhibitor of **HIV**-1 Protease: Computational Analysis and X-ray Crystal Structure of the Enzyme Complex
AUTHOR(S): Smith III, Amos B.; Hirschmann, Ralph; Pasternak, Alexander; Yao, Wenquing; Sprengeler, Paul A.; Holloway, M. Katharine; Kuo, Lawrence C.; Chen, Zhongguo; Darke, Paul L.; Schleif, William A.
CORPORATE SOURCE: Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: J. Med. Chem. (1997), 40(16), 2440-2444
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The design and synthesis of **HIV**-1 protease inhibitors based upon the 2,5,5-trisubstituted pyrrolin-4-one scaffold are described. Reduced mol. wts. compared with our earlier bispyrrolinones, were expected to result in improved pharmacokinetic properties. Indeed, though less active than analogous amide-based inhibitors against the purified enzyme, the monopyrrolinones possess superior cellular transport properties as indicated by lower CIC95/IC50 ratios. The most potent inhibitor (I) displayed 13% oral bioavailability in dogs. X-ray anal. of I cocrystd. with the enzyme revealed an unexpected H-bond to Asp25 as well as binding

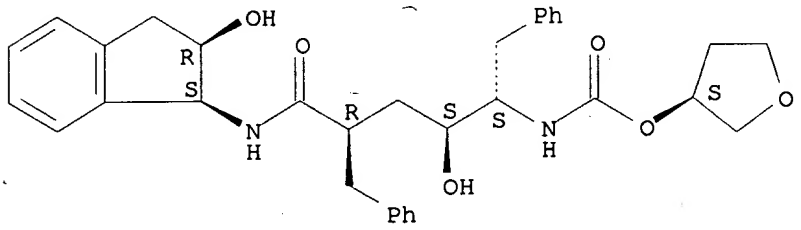
of a water mol. in the active site. Comparison with the similar complex of the amide inhibitor Crixivan showed displacement of the protease backbone to accommodate the pyrrolinone ring, accompanied by variation in H-bonding and more subtle conformational changes in other regions of the enzyme.

IT **145631-03-4**, L 697807
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally bioavailable pyrrolinone inhibitor of **HIV**-1 protease, with computational anal. and X-ray crystal structure of enzyme complex)

RN 145631-03-4 CA

CN Carbamic acid, [(1S,2S,4R)-5-[[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, (3S)-tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145631-03-4**, L 697807
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally bioavailable pyrrolinone inhibitor of **HIV**-1 protease, with computational anal. and X-ray crystal structure of enzyme complex)

L8 ANSWER 5 OF 12 CA COPYRIGHT 2000 ACS

ACCESSION NUMBER: 125:104292 CA

TITLE: A Priori Prediction of Activity for **HIV**-1 Protease Inhibitors Employing Energy Minimization in the Active Site. [Erratum to document cited in CA122:177664]

AUTHOR(S): Holloway, M. Katharine; Wai, Jenny M.; Halgren, Thomas A.; Fitzgerald, Paula M. D.; Vacca, Joseph P.; Dorsey, Bruce D.; Levin, Rhonda B.; Thompson, Wayne J.; Chen, L. Jenny; et al.

CORPORATE SOURCE: Department of Molecular Systems, Merck Research Laboratories, West Point, PA, 19486, USA

SOURCE: J. Med. Chem. (1996), 39(11), 2280
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Equations 1-3 are cor. The errors were not reflected in the abstr. or the index entries.

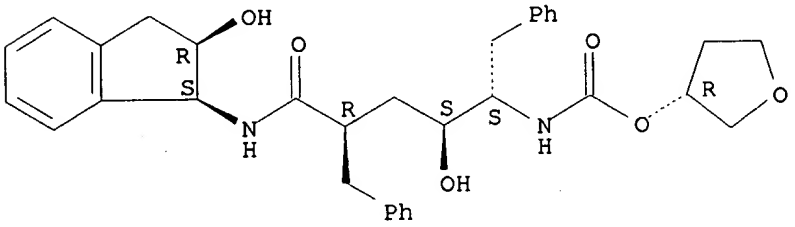
IT **145680-03-1**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)

(energy minimization in active site for design of **HIV**-1 protease inhibitors (Erratum))

RN 145680-03-1 CA

CN Carbamic acid, [5-[(2,3-dihydro-2-hydroxy-1H-inden-1-yl)amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, tetrahydro-3-furanyl ester, [1S-[1.alpha.[1R*(S*),2R*,4S*],2.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145680-03-1**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(energy minimization in active site for design of **HIV**-1 protease inhibitors (Erratum))

L8 ANSWER 6 OF 12 CA COPYRIGHT 2000 ACS

ACCESSION NUMBER: 125:59130 CA

TITLE: Preparation of ethers of aspartate protease substrate isosteres as antivirals.

INVENTOR(S): Bold, Guido; Capraro, Hans-Georg; Faessler, Alexander; Lang, Marc; Bhagwat, Shripad Subray; Khanna, Satish Chandra; Lazdins, Janis Karlis; Mestan, Juergen

PATENT ASSIGNEE(S): Ciba-Geigy A.-G., Switz.

SOURCE: Eur. Pat. Appl., 131 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

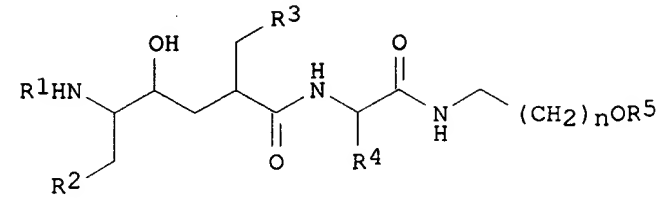
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 708085	A2	19960424	EP 1995-115938	19951010
EP 708085	A3	19971008		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AU 9534279	A1	19960502	AU 1995-34279	19951012
AU 707283	B2	19990708		
FI 9504913	A	19960420	FI 1995-4913	19951016
CA 2160763	AA	19960420	CA 1995-2160763	19951017
ZA 9508782	A	19960419	ZA 1995-8782	19951018
NO 9504142	A	19960422	NO 1995-4142	19951018
CN 1132756	A	19961009	CN 1995-120506	19951018
HU 74744	A2	19970228	HU 1995-3007	19951018
JP 08208580	A2	19960813	JP 1995-295024	19951019
BR 9504466	A	19970520	BR 1995-4466	19951019
US 5663200	A	19970902	US 1995-545170	19951019
US 5807891	A	19980915	US 1997-838347	19970408

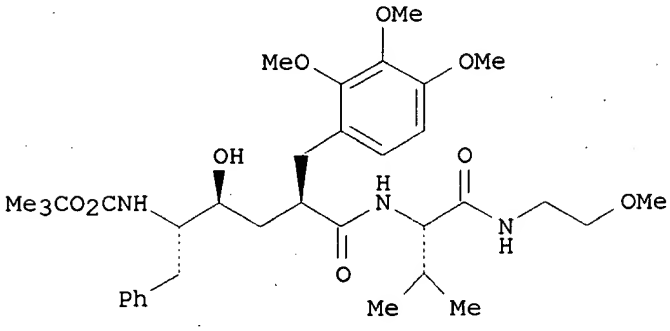
US 5935976 A 19990810 US 1998-138076 19980821
PRIORITY APPLN. INFO.: CH 1994-3140 19941019
CH 1995-2382 19950821
US 1995-545170 19951019
US 1997-838347 19970408

OTHER SOURCE(S): MARPAT 125:59130

GI



I



II

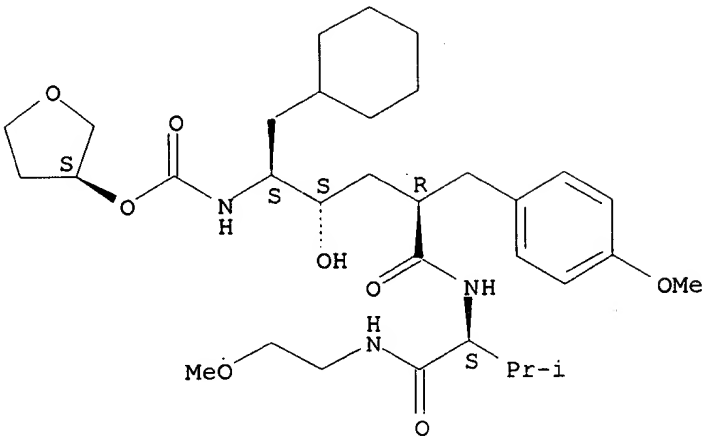
AB Title compds. [I; R1 = (substituted) alkoxyalkanoyl, alkoxycarbonyl, alkanoyl, arylcarbonyl, heterocyclylcarbonyl, phenylalkanoyl, arylsulfonyl, amino acid residue; R2, R3 = (substituted) cyclohexyl, cyclohexenyl, Ph, naphthyl, tetrahydronaphthyl; R4 = alkyl, cyclohexyl, Ph; R5 = alkyl; n = 1, 2; provided .gtoreq.1 salt forming group is present], were prepd. Thus, title compd. (II), prepd. via 5(S)-[1(S)-(tert-butoxycarbonylamino)-2-phenylethyl]-3(R)-[(2,3,4-trimethoxyphenyl)methyl]dihydrofuran-2(3H)-one, at 12.5 nM combined with 12.5 nM indavir gave 76.6% inhibition of reverse transcriptase in a coculture of CEM-SS and H9/**HIV**-1/IIIB. Capsule formulations contg. II are given.

IT **178048-12-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ethers of aspartate protease substrate isosteres as antivirals)

RN 178048-12-9 CA

CN 2-Oxa-5,8,14-triazapentadecan-15-oic acid, 13-(cyclohexylmethyl)-12-hydroxy-10-[(4-methoxyphenyl)methyl]-7-(1-methylethyl)-6,9-dioxo-, tetrahydro-3-furanyl ester, [3S-[3R*(7R*,10S*,12R*,13R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **178048-12-9P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ethers of aspartate protease substrate isosteres as antivirals)

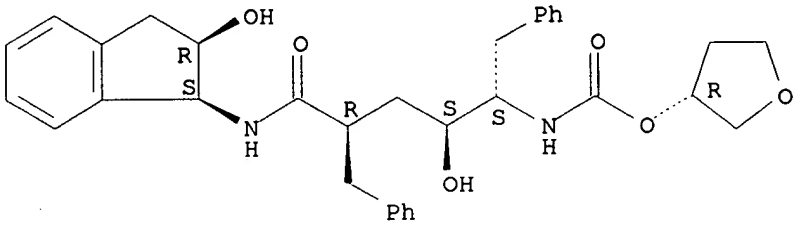
L8 ANSWER 7 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 122:177664 CA
TITLE: A priori prediction of activity for **HIV**-1 protease inhibitors employing energy minimization in the active site
AUTHOR(S): Holloway, M. Katharine; Wai, Jenny M.; Halgren, Thomas A.; Fitzgerald, Paula M. D.; Vacca, Joseph P.; Dorsey, Bruce D.; Levin, Rhonda B.; Thompson, Wayne J.; Chen, L. Jenny; et al.
CORPORATE SOURCE: Department of Molecular Systems, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: J. Med. Chem. (1995), 38(2), 305-17
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A high correlation was obsd. between the intermol. interaction energy (Einter) calcd. for **HIV**-1 protease inhibitor complexes and the obsd. in vitro enzyme inhibition. A training set of 33 inhibitors contg. modifications in the P1' and P2' positions was used to develop a regression equation which relates Einter and pIC50. This correlation was subsequently employed to successfully predict the activity of proposed **HIV**-1 protease inhibitors in advance of synthesis in a structure-based design program. This included a precursor to the current phase II clin. candidate L-735,524. The development of the correlation, its applications, and its limitations are discussed, and the force field (MM2X) and host mol. mechanics program (OPTIMOL) used in this work are described.

IT **145680-03-1**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(energy minimization in active site for design of **HIV**-1

protease inhibitors)
RN 145680-03-1 CA
CN Carbamic acid,
[5-[(2,3-dihydro-2-hydroxy-1H-inden-1-yl)amino]-2-hydroxy-5-
oxo-1,4-bis(phenylmethyl)pentyl]-, tetrahydro-3-furanyl ester,
[1S-[1.alpha.[1R*(S*),2R*,4S*],2.alpha.]]- (9CI) (CA INDEX NAME)

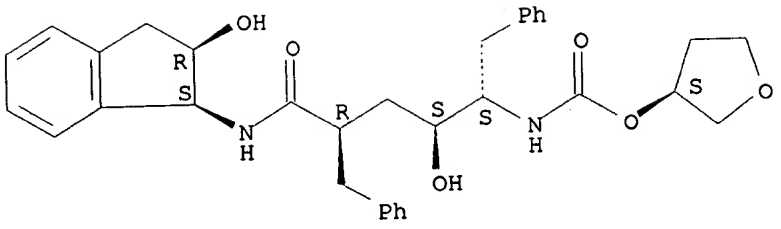
Absolute stereochemistry.



IT **145680-03-1**
RL: BAC (Biological activity or effector, except adverse); PRP
(Properties); BIOL (Biological study)
(energy minimization in active site for design of **HIV**-1
protease inhibitors)

L8 ANSWER 8 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 121:218 CA
TITLE: Conformationally constrained **HIV**-1 protease inhibitors
AUTHOR(S): Vacca, J. P.; Fitzgerald, P. M. D.; Holloway, M. K.; Hungate, R. W.; Starbuck, K. E.; Chen, L. J.; Darke, P. L.; Anderson, P. S.; Huff, J. R.
CORPORATE SOURCE: Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Bioorg. Med. Chem. Lett. (1994), 4(3), 499-504
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The synthesis and structure activity relationships of conformationally constrained analogs of the **HIV**-1 protease inhibitor L-685,434 are described. In addn., the x-ray crystal structure of a complex between
L-700,497 and the **HIV**-1 protease is shown.
IT **145631-03-4**
RL: BIOL (Biological study)
(**HIV**-1 protease inhibition by, structure in relation to)
RN 145631-03-4 CA
CN Carbamic acid, [(1S,2S,4R)-5-[[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, (3S)-tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145631-03-4**
RL: BIOL (Biological study)
(**HIV**-1 protease inhibition by, structure in relation to)

L8 ANSWER 9 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 119:250516 CA
TITLE: Dipeptide isosteres as **HIV** protease inhibitors useful for the treatment of AIDS
INVENTOR(S): Ghosh, Arun K.; Huff, Joel R.; Thompson, Wayne J.; Lyle, Terry A.; Hungate, Randall W.; McKee, Sean P.; Lee, Hee Y.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Can. Pat. Appl., 100 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2075666	AA	19930217	CA 1992-2075666	19920810
EP 534511	A1	19930331	EP 1992-202447	19920808
R: CH, DE, FR, GB, IT, LI, NL				
JP 05222020	A2	19930831	JP 1992-215257	19920812
			US 1991-746686	19910816

PRIORITY APPLN. INFO.:
OTHER SOURCE(S): MARPAT 119:250516
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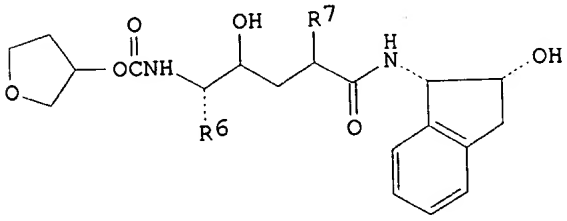


I

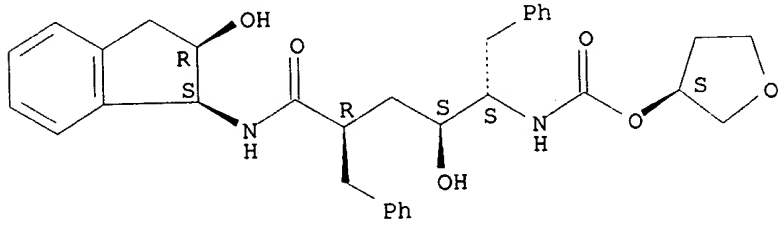
AB Title compds. A-G-J [A = a variety of organooxycarbonyl groups R1R2R3CO2C, preferably tetrahydrofuranyloxycarbonyl or tetrahydropyranyloxycarbonyl; G = a dipeptide isostere -NHCHR6QCHR7CO- or -NHCHR6CHR8Q'CO- where Q = CH(OH)CH2, CH(OH), or CH(OH)CH(OH) and Q' = various (un)substituted C3-7 cycloalkyls; J = small terminal group, e.g., NHR11, halo, OR, CO2R, etc.]

are prepd. and are **HIV** protease inhibitors. Thus, title compds., e.g., hexanamide I (R6 = CH2Ph, R7 = CH2C6H4OCH2CH2OH-4), are prepd. by well-known procedures for prepg. peptide analogs. Once the G substituent is made, the rest of the synthesis follows the principle of amide bond formation by coupling methods of either soln.-phase or solid-phase peptide synthesis. The compds., their pharmaceutically acceptable salts or esters, isomers, and pharmaceutical compns. are useful for the prevention or treatment of infection by **HIV** and for the treatment of AIDS or ARC (AIDS Related Complex). The compds. showed IC50 values of 0.1 nM - 100 .mu.M for inhibition of microbial expressed viral protease with preferred species having activities of 0.37 and 0.04 nM. Examples of possible pharmaceutical combinations of the compds. with other agents useful in the treatment of AIDS are given.

IT **145631-03-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV** protease inhibitor useful for the treatment of AIDS)

RN 145631-03-4 CA
CN Carbamic acid, [(1S,2S,4R)-5-[[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, (3S)-tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145631-03-4P 151177-02-5P 151177-03-6P 151177-04-7P 151177-05-8P 151177-06-9P 151177-07-0P 151177-08-1P 151177-29-6P 151177-32-1P 151177-34-3P 151177-35-4P 151177-36-5P 151177-37-6P 151177-38-7P 151177-39-8P 151177-40-1P 151177-41-2P 151177-42-3P 151177-43-4P 151177-46-7P 151177-47-8P 151177-48-9P 151177-49-0P 151177-50-3P 151177-53-6P 151177-55-8P 151177-59-2P 151283-40-8P 151283-41-9P 151283-42-0P 151283-50-0P 151283-51-1P 151283-52-2P 151283-53-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV** protease inhibitor useful for the treatment of AIDS)

IT **151177-33-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for dipeptide isostere **HIV** protease inhibitor)

L8 ANSWER 10 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 119:203319 CA
TITLE: Preparation of decahydroisoquinolinecarboxamides as

HIV protease inhibitors

INVENTOR(S): Thompson, Wayne J.; Ghosh, Arun K.; Lee, Hee Yoon; Huff, Joel R.

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 539192	A1	19930428	EP 1992-309639	19921021
EP 539192	B1	19990107		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
WO 9308184	A1	19930429	WO 1992-US8758	19921014
W: BG, CS, FI, HU, KR, NO, PL, RO, RU				
AT 175412	E	19990115	AT 1992-309639	19921021
ES 2125251	T3	19990301	ES 1992-309639	19921021
CA 2081134	AA	19930424	CA 1992-2081134	19921022
AU 9227253	A1	19930429	AU 1992-27253	19921022
AU 649170	B2	19940512		
ZA 9208164	A	19930503	ZA 1992-8164	19921022
JP 05239031	A2	19930917	JP 1992-309474	19921023
JP 06078314	B4	19941005		
US 5502060	A	19960326	US 1994-328936	19941025
			US 1991-781470	19911023
			US 1992-929991	19920821
			US 1993-144094	19931027

PRIORITY APPLN. INFO.:

OTHER SOURCE(S): MARPAT 119:203319

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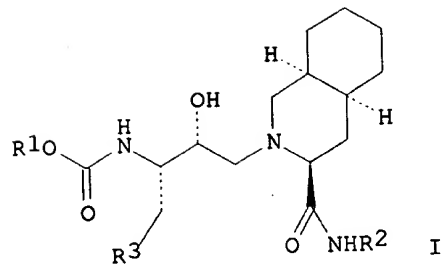

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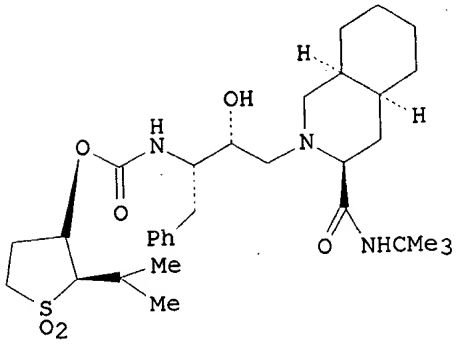


II

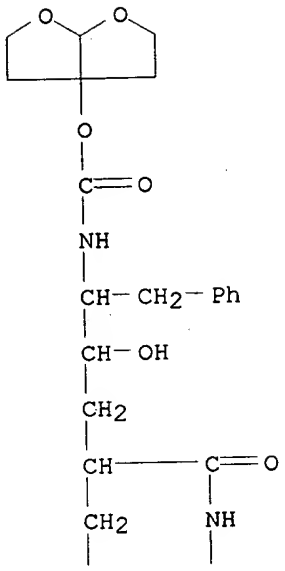
AB Title compds. [I; R1 = (unsatd.) (substituted) 5-7 membered carbocyclyl, heterocyclyl; R2 = (substituted) alkyl, (substituted) (unsatd.) 5-7 membered carbocyclyl; R3 = (substituted) Ph, cycloalkyl], were prepd. Thus, 2(R,S)-methylethyl-3(R,S)-tetrahydrothienyl 2-pyridyl carbonate (prepn. given) and N-tert-Bu decahydro-2-(2R-hydroxy-4-phenyl-3S-aminobutyl)-(4aS,8aS)-isoquinoline-3S-carboxamide (prepn. given) were stirred with Et3N in CH2Cl2 to give the diamide, which was S-oxidized with N-methylmorpholine oxide/OsO4 in actone/H2O/Me3COH to give, after chromatog., title compd. II. II inhibited **HIV** protease with IC50 = 4 nM.

IT **138484-79-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for isoquinolinecarboxamide deriv. **HIV** protease inhibitor)

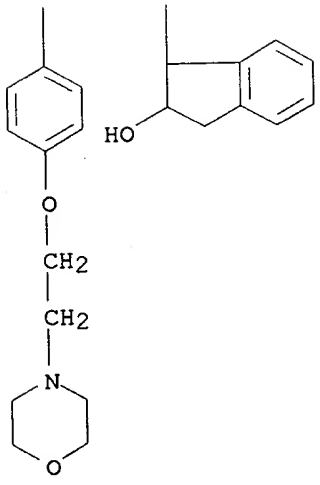
RN 138484-79-4 CA

CN Carbamic acid, [5-[(2,3-dihydro-2-hydroxy-1H-inden-1-yl)amino]-2-hydroxy-4-[[4-[2-(4-morpholinyl)ethoxy]phenyl]methyl]-5-oxo-1-(phenylmethyl)pentyl]-, tetrahydrofuro[2,3-b]furan-3a(6aH)-yl ester, [1S-[1.alpha.(1R*,2R*,4S*),2.alpha.]]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



IT **138484-79-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for isoquinolinecarboxamide deriv. **HIV** protease inhibitor)

L8 ANSWER 11 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 118:75966 CA
TITLE: 3-Tetrahydrofuran and pyran urethanes as high-affinity

P2-ligands for **HIV**-1 protease inhibitors

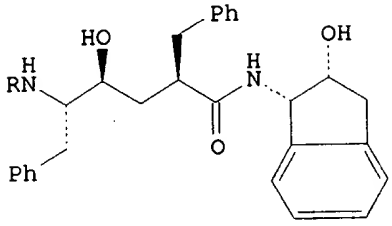
AUTHOR(S): Ghosh, Arun K.; Thompson, Wayne J.; McKee, Sean P.; Duong, Tien T.; Lyle, Terry A.; Chen, Jenny C.; Darke, Paul L.; Zugay, Joan A.; Emini, Emilio A.; et al.

CORPORATE SOURCE: Dep. Med. Chem., Merck Res. Lab., West Point, PA, 19486, USA

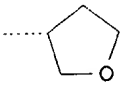
SOURCE: J. Med. Chem. (1993), 36(2), 292-4
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal
LANGUAGE: English

GI



I, R=CO_2CMe_3



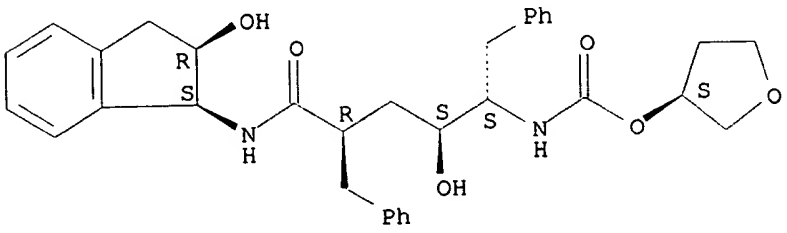
II, R=CO_2

AB Urethanes of 3-tetrahydrofurans and pyrans are high affinity P2 ligands for the **HIV**-1 protease inhibitors. Incorporation of these ligands provided potent inhibitors in the hydroxyethylene and hydroxyethylamine series with picomolar and nanomolar in vitro potencies. Substitution of t-butyloxycarbonyl group in I either with 3-tetrahydrofuranyl or 3-tetrahydropyranyl urethane not only increases intrinsic potency against the enzyme but generally leads to significant enhancement of antiviral potency as well. For example, II (IC50 <0.03 nM), obtained from com. available 3-(S)-hydroxytetrahydrofuran has prevented the spread of **HIV**-1 at a concn. of 3 nM (CIC95), a greater than 133-fold potency enhancement over inhibitor I.

IT **145631-03-4**
RL: BIOL (Biological study)
(aspartic proteinase of **HIV**-1 virus inhibition by, structure in relation to)

RN 145631-03-4 CA
CN Carbamic acid, [(1S,2S,4R)-5-[[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]amino]-2-hydroxy-5-oxo-1,4-bis(phenylmethyl)pentyl]-, (3S)-tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145631-03-4 145680-03-1**
RL: BIOL (Biological study)
(aspartic proteinase of **HIV**-1 virus inhibition by, structure in relation to)

L8 ANSWER 12 OF 12 CA COPYRIGHT 2000 ACS
ACCESSION NUMBER: 116:256051 CA
TITLE: Preparation of dipeptide isosters
INVENTOR(S): Thompson, Wayne J.; Vacca, Joseph P.; Huff, Joel R.; Lyle, Terry A.; Young, Steven D.; Hungate, Randall W.; Britcher, Susan F.; Ghosh, Arun K.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 101 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

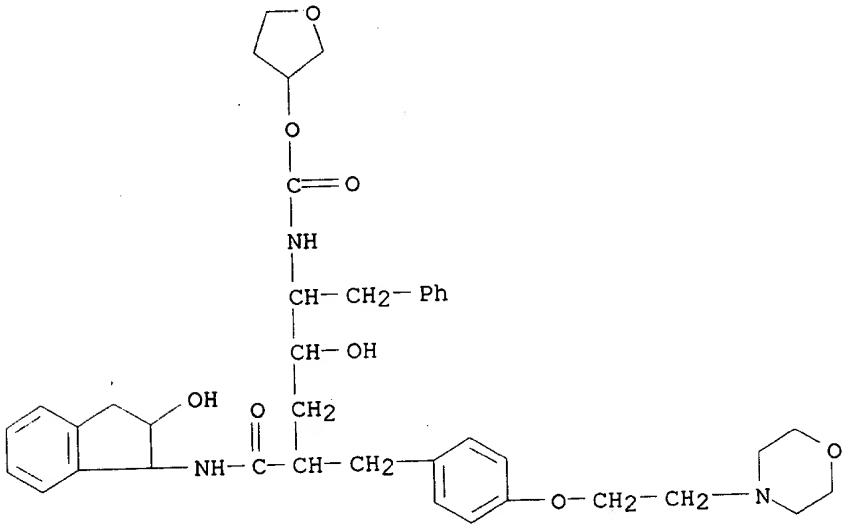
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 434365	A2	19910626	EP 1990-313848	19901218
EP 434365	A3	19911127		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2032259	AA	19910619	CA 1990-2032259	19901214
FI 9006212	A	19910619	FI 1990-6212	19901217
NO 9005428	A	19910619	NO 1990-5428	19901217
ZA 9010125	A	19910925	ZA 1990-10125	19901217
AU 9068229	A1	19910627	AU 1990-68229	19901218
CN 1053607	A	19910807	CN 1990-110446	19901218
JP 05345775	A2	19931227	JP 1990-419337	19901218
PRIORITY APPLN. INFO.:			US 1989-452912	19891218
			US 1990-597286	19901015
			US 1990-619654	19901204

OTHER SOURCE(S): MARPAT 116:256051
GI For diagram(s), see printed CA Issue.
AB A-G-B-B1-J [I; A = H, alkanoyl, alkenoyl, alkylsulfonyl, (substituted) sulfamoyl, (substituted) carbamoyl, alkylthiocarbonyl, (substituted) methoxycarbonyl; G = NHCHR9X1CHR10C(Z), NHCHR9CHR15XCO; R9, R10 = (substituted) alkyl, alkenyl, etc.; R15 = OH, (substituted) amino; Z = O, S, H2; X = (substituted) cycloalkylene; X1 = CH(OH)CH2, CH2NH, CH(NH2), etc.; B, B1 = null, NHCR21C(Z); R21 = Me2CH, CHMeEt, Ph; J = OH, alkoxy, (substituted) amino] were prepd. Hexanoic acid deriv. II [R1 = OH, R2 = benzyl, R4 = SiMe2CMe3] (prepd. in many steps) was condensed with aminoindanol QH in DMF contg. 1-hydroxybenzotriazole hydrate, ethyl[3-(dimethylamino)propyl]carbodiimide hydrochloride, and Et3N, the product treated with a mixt. of citric acid, H2O, and NaHCO3, and the mixt. stirred with Bu4NF in THF overnight to give II [R1 = Q, R2 = benzyl, R4 - H], which was hydrogenolyzed over Pt/C to give II [R1 = Q, R2 = R4 = H], whose condensation with N-(2-chloroethyl)morpholine in dioxane contg. Cs2CO3 gave title compd. II [R1 = Q, R2 = 2-morpholinoethyl, R4 = H] (III). In a study on the inhibition of the reaction of the protease expressed in Escherichia coli with a peptide substrate [H-Val-Ser-Gln-Asn-(.beta.-naphthyl)Ala-Pro-Ile-Val-OH] III had an IC50 of 0.1-10 nM.
IT **138484-36-3P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV** inhibitor)

RN 138484-36-3 CA

CN Carbamic acid,
[5-[(2,3-dihydro-2-hydroxy-1H-inden-1-yl)amino]-2-hydroxy-4-
[[4-[2-(4-morpholinyl)ethoxy]phenyl]methyl]-5-oxo-1-(phenylmethyl)pentyl]-
, tetrahydro-3-furanyl ester (9CI) (CA INDEX NAME)



IT **138484-36-3P 138484-79-4P 138498-30-3P**
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138498-34-7P 138498-35-8P 138498-36-9P
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138603-43-7P 138603-44-8P 138603-45-9P
138603-46-0P 138603-47-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as **HIV** inhibitor)

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L3 0 S L1 FULL

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L6           66 S L4 FULL

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L9            0 S L1 SAM
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